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EDITORIAL

Light from DARCness

The recruitment of leukocytes during host defense and inflammation is a complex process involving the coordinated interactions of leukocyte adhesion molecules and chemoattractants [1–4]. Included among the latter chemoattractant molecules are the chemokines, a superfamily of small (~8–13 kD) secreted cytokines [3, 4]. The characterization of key molecular determinants of leukocyte trafficking in renal disease has already identified a range of attractive new therapeutic targets in glomerulonephritis, tubulointerstitial nephritis, ischemic acute renal failure and allograft rejection [2, 4]. Several agents that block chemokine and adhesion molecule expression or function have already been shown to confer impressive protection in experimental models of renal inflammation [2, 4]. It is clear, however, that many important players have yet to be defined and that, in an environment where there is frequently overlap of function, the hierarchy of mediators has yet to be fully established.

In this issue of *Kidney International* Segerer et al report important new data on the expression of an intriguing chemokine receptor identified relatively recently, namely Duffy antigen receptor for chemokines (DARC) [5]. The history of DARC is a glowing tribute to investigators exploring remarkably diverse topics [reviewed extensively in 6]. Following the initial identification of chemokines and adhesion molecules as pivotal regulators of leukocyte recruitment during host defense and inflammation, it became apparent that many microorganisms (such as HIV, rhinovirus) infect host cells by usurping the function of chemokine receptors and adhesion molecules [1–4]. With respect to DARC, the order of discovery was reversed [6]. DARC was originally described as the Duffy antigen, a glycoprotein blood group antigen expressed on the surface of erythrocytes that is a receptor for invasion of these cells by the malarial parasite *Plasmodium vivax.* Erythrocytes from individuals of the Duffy antigen-negative phenotype are resistant to infection by *P. vivax* merozoites and *P. vivax* infection is virtually completely absent from West Africa where greater than 95% of the population are Duffy antigen-negative, unlike most other tropical and subtropical regions where this infection is prevalent [6]. Subsequently, a novel chemokine receptor was identified on erythrocytes with high affinity for the C-X-C chemokines interleukin-8 (IL-8) and melanoma growth stimulatory activity (MGSA) and for the C-C chemokines RANTES and monocyte chemotactic peptide-1 (MCP-1). Detailed analysis of this novel chemokine receptor revealed that it is identical to DARC [6].

The immunohistochemical demonstration of DARC expression on endothelial cells lining post-capillary venules, but not endothelium of most other vessels, shed new light on the biology of DARC [6]. Endothelial DARC expression is observed even in individuals with the Duffy antigen-negative erythroid phenotype suggesting cell-type specific regulation of gene transcription. Curiously DARC expression has also been described under normal conditions by cerebellar Purkinje cells [6]. Up-regulation of DARC expression has been reported on glomerular endothelium, collecting duct cells and interstitial cells in children with HIV-associated nephropathy, HIV-associated hemolytic uremic syndrome and classic hemolytic uremic syndrome [7], and on the endothelium of large vessels in temporal arteritis and thrombophlebitis [6]. When coupled with the ability of DARC to bind C-C and C-X-C cytokines, these observations raise the possibility of an immunomodulatory role for DARC in inflammatory diseases. Against this background, in this issue Segerer et al report a marked increase in DARC positive venules in the renal interstitium during transplant rejection and crescentic glomerulonephritis, in association with an infiltration of CCR5 positive leukocytes [5]. DARC was not expressed in the glomerulus, even in crescentic glomerulonephritis [5]. They propose that DARC may serve to present chemokines to CCR5 positive cells in this context and thereby promote leukocyte recruitment into the tubulointerstitium. Their contention is further supported by the following observations: (*a*) the concept of chemokine presentation to leukocytes is a well-validated paradigm in chemokine research; (*b*) post-capillary venules are a major site for leukocyte extravasation in host defense and disease; and (*c*) DARC null mice show impaired neutrophil migration in lipopolysaccharide and thioglycolate induced models of peritonitis in vivo [1–4, 8].

Importantly, however, Segerer and colleagues do not dismiss a possible anti-inflammatory role whereby DARC could serve as a "sink" for removal of chemokines during inflammation [5]. Indeed, several lines of evidence support an anti-inflammatory role for DARC: (*a*) IL-8 is

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not chemotactic for polymorphonuclear neutrophils once bound to the erythrocyte surface, thereby arguing against a "presenting" function; (*b*) DARC transfectants internalize chemokine ligands, although it should be noted that DARC positive erythrocytes do not; and (*c*) DARC-triggered cell signaling has yet to be demonstrated, and DARC lacks both the DRY motif and the second cytoplasmic loop characteristic of G-protein-coupled seven transmembrane spanning receptors and the ability to stimulate GTPase activity [6,9].

As with all important reports, the contribution by Segerer et al adds significantly to existing knowledge and raises interesting new questions. The further study of the putative pro- and anti-inflammatory roles of DARC in renal disease should not only illuminate our understanding of mechanisms of tubulointerstitial inflammation, but may also suggest new treatment strategies. The inflammatory mediators and signaling pathways responsible for induction of DARC expression have yet to be identified. Indeed, the identification of regiospecific endothelial expression of inducible proteins such as DARC underscores the heterogeneity of renal endothelium. The dissection of transcriptional regulatory pathways and other modulators of regiospecific protein expression within the kidney is likely to have implications for gene therapy. Finally, the functional significance of DARC expression in non-endothelial cells both within the kidney and at extrarenal sites remains to be explored, and should shed further light on the role of DARC in health and disease.

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